IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Stace Lindsay et al.	Confirmation No.:	8638
Serial No.:	10/030,351	Art Unit:	1632
Filed:	June 7, 2002	Examiner:	Valarie E. Bertoglio
Customer No.:	21559		
Title:	EXPRESSION OF SECRETED HUMAN ALPHA-FETOPROTEIN IN TRANSGENIC ANIMALS		

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants respectfully request review of the above-referenced application prior to the filing of an Appeal Brief. Applicants submit the request for review in lieu of a reply to the non-final Office Action dated January 30, 2008. This request is being filed with a Notice of Appeal.

The review is requested for the reasons stated on the attached sheets.

Applicants request review of the rejections made in the non-final Office Action dated January 30, 2008.

I. Claims 6, 7, 21-24, and 27 do not Contain New Matter and are Fully Enabled

New Matter

The Office states that addition of the phrase "biologically active" to claims 6, 21, and 23 introduces new matter because "[l]iteral support for this terminology is not found in the specification" (Office Action, p. 2). Applicants respectfully traverse this rejection and request its withdrawal.

Support for the phrase "biologically active" in claims 6, 21, and 23 can be found in the specification at, e.g., page 5, lines 8-11, and page 9, lines 12-17, which describes a method of treating a patient by administering a therapeutically-effective amount of a non-human mammal's milk containing recombinant human alpha-fetoprotein (rHuAFP); the rHuAFP can be administered "for the treatment of cancer, for suppressing the immune system, or for inducing proliferation of bone marrow cells in a patient in need thereof"(page 5, lines 8-11, of the specification). A therapeutically-effective amount of rHuAFP is defined in the present specification as

> an amount of recombinant human alpha-fetoprotein or fragment thereof that when administered to a patient inhibits or stimulates a biological activity modulated by human alpha-fetoprotein. Such biological activities include inhibiting the proliferation of a neoplasm or an autoreactive immune cell, or stimulating proliferation of a cell (*e.g.*, a bone marrow cell).

Although the term "biologically active" rHuAFP does not literally appear in the present specification, *ipsis verbis* disclosure is not necessary to satisfy the written description requirement of 35 U.S.C. § 112. The disclosure need only reasonably convey to persons skilled in the art that the inventors had possession of the subject matter in question (*In re Edwards*, 568 F.2d 1349, 1351-52, 196 U.S.P.Q. (BNA) 465, 467 (CCPA 1978) and *In re Smythe*, 480 F.2d 1376, 1383-84, 178 U.S.P.Q. (BNA) 279 (CCPA 1973)). The specification teaches that rHuAFP, which is present in or purified from the milk of a transgenic mammal engineered to express

rHuAFP in its milk, can be administered therapeutically. Treatment, which occurs upon the administration of a "therapeutically effective amount" of rHuAFP, is a result of the biological activity of human alpha-fetoprotein. This understanding would naturally occur to one skilled in the art from reading Applicants' description of the use and functions of rHuAFP that has been expressed by a transgenic mammal. For these reasons, the phrase "biologically active" does not introduce new matter to claims 6, 21, and 23. The rejection of claims 6, 7, 21-24, and 27 for new matter can be withdrawn.

Enablement

The Office further states:

> *To the extent that the claimed compositions and/or methods are not described in the instant disclosure*, claims 6, 7, 21-24, and 27 are also rejected under 35 U.S.C. 112, first paragraph, [for lack of enablement]...since a disclosure cannot teach one to make or use something that has not been described" (Office Action, p. 3; emphasis added).

Thus, the enablement rejection of claims 6, 7, 21-24, and 27 is predicated on the lack of written description in the specification. Because the subject matter of present claims 6, 21, and 23 is fully supported in the present specification, for the reasons given above, the basis given by the Office for the enablement rejection of claims 6, 7, 21-24, and 27 no longer applies. For this reason, the rejection of claims 6, 7, 21-24, and 27 for lack of enablement should be withdrawn.

II. Claims 25-27 do not Lack Written Description

The Office also rejects claims 25-27 under 35 U.S.C. § 112, first paragraph, for lack of written description (Office Action, pp. 3-4). This rejection is clearly in error and should be withdrawn. As is acknowledged by the Office in the present Office Action, the specification clearly describes a transgene that can be modified to express a non-glycosylated rHuAFP (see, e.g., page 12, line 25, through page 13, line 1). Nothing more is required to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. This rejection should be withdrawn.

III. Claims 1, 6, 7, and 21-27 are not Obvious over DeBoer, Clark, or Lubon in View of Morinaga and Bennett

The Office rejects claims 1, 6, 7, and 21-27 under 35 U.S.C. § 103(a) over DeBoer, Clark or Lubon in view of Morinaga and Bennett. This rejection should be withdrawn for the reasons

stated in the Reply to Final Office Action filed on October 30, 2007 (the "Reply", which is incorporated by reference).

The Office states that "Deboer, Clark, and Lubon render making any protein of interest obvious in the absence of evidence to the contrary" (see page 7, Office Action dated January 30, 2008; the "Office Action"). The evidence of non-obviousness provided by Applicants in the Reply demonstrates that skilled artisans, prior to the filing date of the present application, confirmed that free fatty acids induce conformational changes in HuAFP that inhibit at least some of its biological activity (see, e.g., pp. 8-10 of the Reply). The cited publications raise substantial doubts about the predictability of expressing *biologically active* rHuAFP in the milk of a transgenic mammal. The Office acknowledges this unpredictability in its attempt to explain away Applicants' evidence, stating:

> First, that some property or properties of rHuAFP *may* be altered by binding or other natural interaction with some fatty acids in milk, does not indicate that all, if any, properties will be affected by the levels of specific fatty acids that are present in milk. Binding of a fatty acid as a ligand would be considered a natural property of AFP and it is not clear that this would be undesirable. It is also noted that Vallette teaches that the identity and quantity of fatty acids present is important in the inhibition of estrogen binding and thus such a variability in the effect of various fatty acids on AFP would likely hold true for other activities of AFP, making it unpredictable which, if any, activities of AFP would be altered in milk. (see Office Action, p. 5; underlining added.)

The Office attempts to diminish the probative weight of Vallette by stating that "the study of Vallette consisted of an unnatural, in vitro situation of incubating AFP with free fatty acids. Neither Applicant nor Vallette provide a nexus between this study and what occurs in vivo in the mammary gland" (Office Action, p. 5).

The Office fails to consider that the expression of rHuAFP in the milk of a transgenic mammal is itself unnatural. Because Vallette and the other cited publications clearly provide evidence of the inhibitory effect of free fatty acids on the biological activity of rHuAFP, when properly considered, these publications, at the least, render a method of producing biologically active rHuAFP fatty acid rich environments, such as milk, unpredictable. In the alternative, the publications cited by Applicants teach away from the invention of present claims 1, 6, 7 and 21-27 (see arguments presented on pp. 8-10 of the Reply).

The Office attempts to dispel the shadow of unpredictability cast by Vallette by stating

that "AFP has been isolated from a number of sources including E. coli, yeast, cord blood and fetal liver and is active in each of these cases" (Office Action, p. 7). The Office concludes by stating that "specific teachings suggesting rHuAFP isolated from milk would not be active are necessary to support an argument that there was not a reasonable expectation of success at filing" (Office Action, p. 7; emphasis added). This position is untenable.

As is discussed above, the Office acknowledges that one cannot predict which, if any, activities of AFP would be altered in milk. Furthermore, the ability to express biologically active rHuAFP in *E. coli*, yeast, cord blood, and fetal liver, none of which contain the large amount of fatty acids that are present in milk, provides no reasonable expectation that the expression of biologically active rHuAFP in milk would be successful. Applicants' evidence raises substantial doubt regarding the predictability of expressing biologically active rHuAFP in fatty acid rich environments, such as the milk of a transgenic mammal. The Office has not properly considered Applicants' evidence and has simply taken the position that present claims 1, 6, 7, and 21-27 are *per se* obvious because expression of any protein in any transgenic mammal is obvious in view of Deboer, Clark, and Lubon.

The M.P.E.P. § 2144.08 (II) makes clear that this position is improper, stating that the "[u]se of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103." Furthermore, when determining whether a claimed species, here the production of rHuAFP in the milk of a transgenic mammal, would have been obvious to one of ordinary skill in the pertinent art at the time the invention was made, the Office must consider the facts of the particular case in view of the totality of the circumstances (M.P.E.P. § 2144.08 (II)); this the Office has failed to do.

In this case, the Office has combined DeBoer, Clark, or Lubon with Morinaga and Bennett without evidence of any suggestion, teaching, or motivation to do so and has disregarded evidence that suggests the unpredictability of, or the teaching away from, the invention of present claims 1, 6, 7, and 21-27. For all of these reasons, Applicants respectfully submit that the rejection of claims 1, 6, 7, and 21-27 under 35 U.S.C. § 103(a) for obviousness over DeBoer, Clark, or Lubon in view of Morinaga and Bennett should be withdrawn.

CONCLUSION

Applicants submit that present claims 1, 6, 7, and 21-27 are in condition for allowance, and such action is respectfully requested.

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Date: 30 April 2008

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